Hormone Therapy, NSAIDs, and the Risk of Dementia

Plus ça change, plus c'est la même chose.

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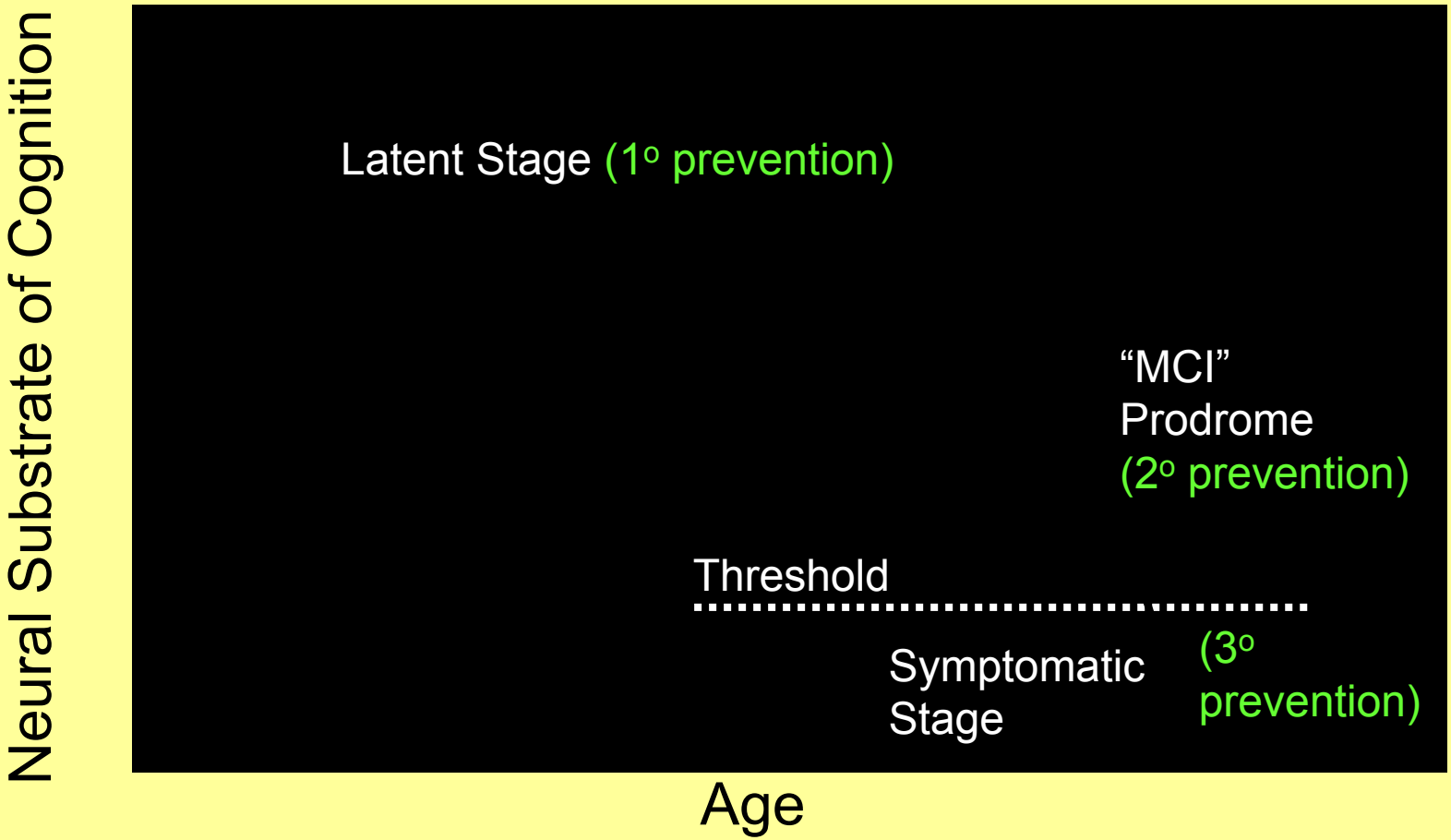
Or . . .

Are Observational Studies Worthless

Or . . .

Does "Nixon's Law" prevail?

Potential Targets for Intervention in AD

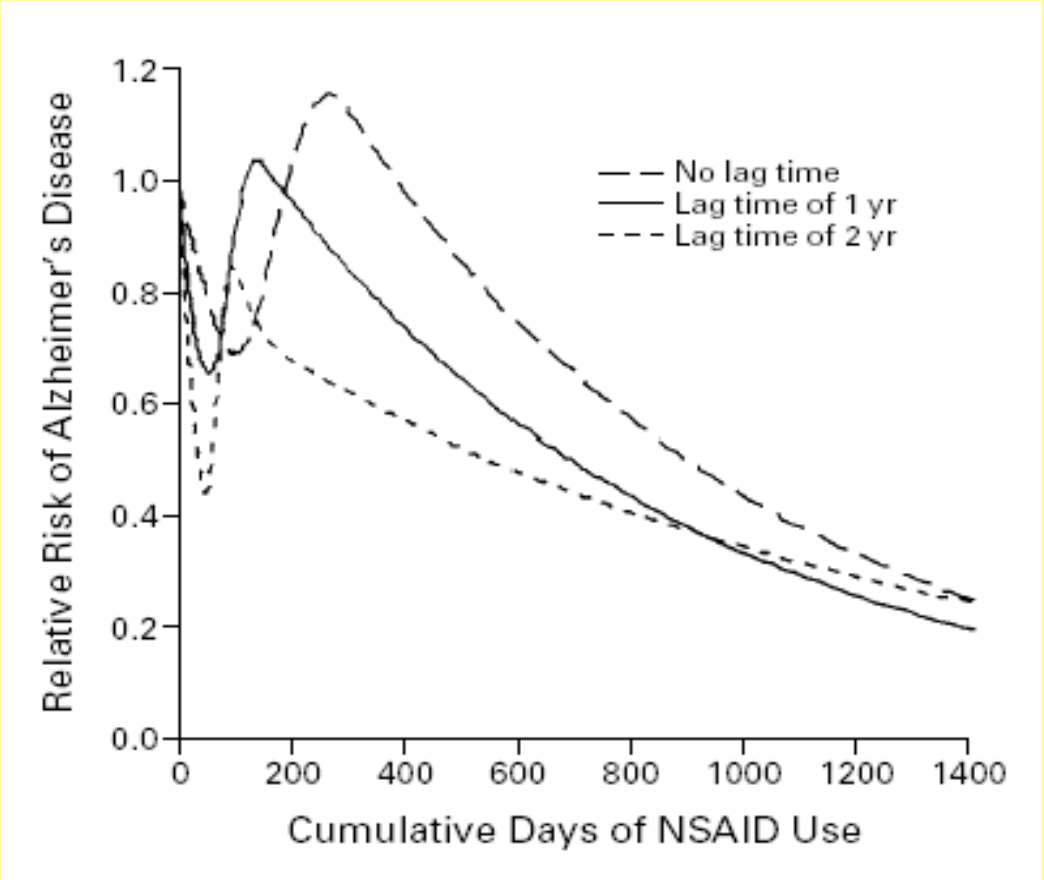


Non-steroidal Anti-inflammatory Treatments and AD

- **At least 25 studies using case-control, case-cohort, and prospective (incidence) designs**
- **7 strong case-control studies with summary odds ratio (OR) 0.51 (95% CI 0.40 - 0.66)**
- **4 population incidence studies, 3 with NSAID Rx duration >2 yrs. Summary hazard ratio (HR) 0.42 (95% CI 0.26 - 0.66)**

Szekely C, et al. Neuroepidemiology, 2004;23:159-69.

Rotterdam Study: Two Year Lag-Time in NSAID "Effect" on Risk of AD.

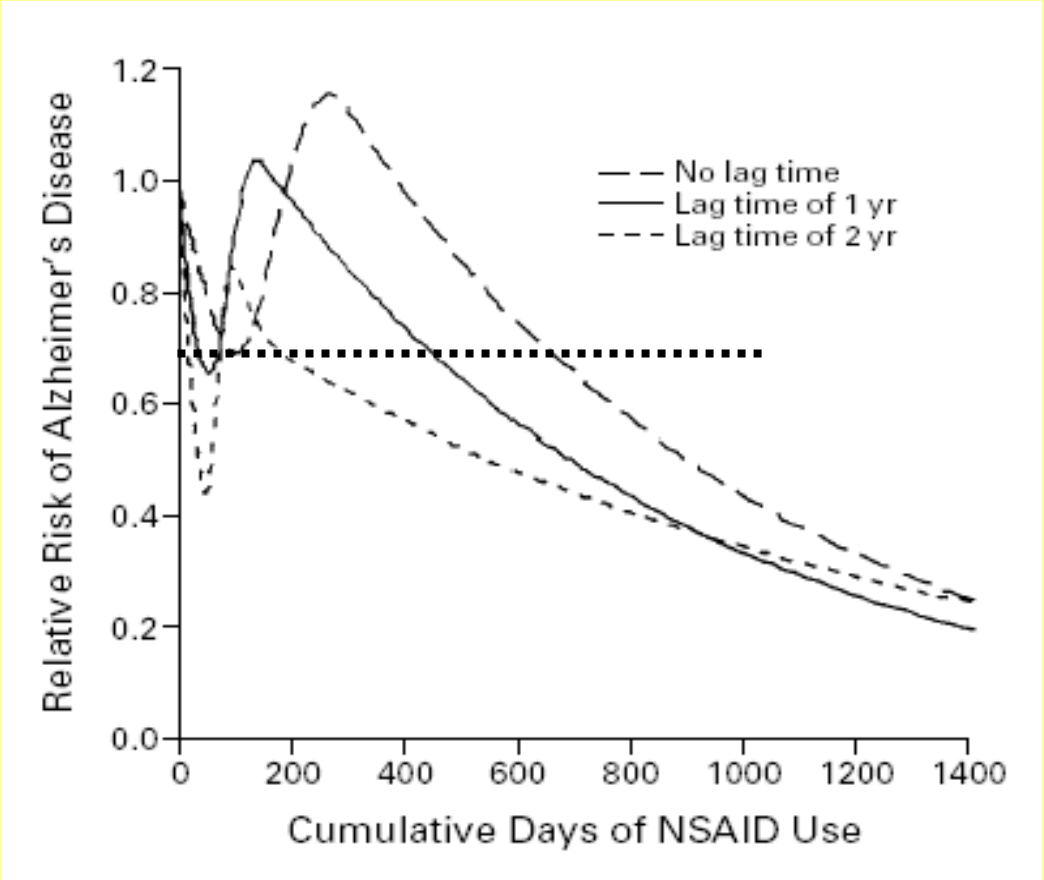


from in't Veld, Stricker, Breteler et al., NEJM, 2001 345:1515-21

Rotterdam Study: Two Year Lag-Time in NSAID "Effect" on Risk of AD.

Dashed line is upper bound of confidence interval from meta-analytic hazard ratio in prospective studies.

from in't Veld, Stricker, Breteler et al., NEJM, 2001 345:1515-21



Cache Co. Study Results
Incidence-Cohort Analyses

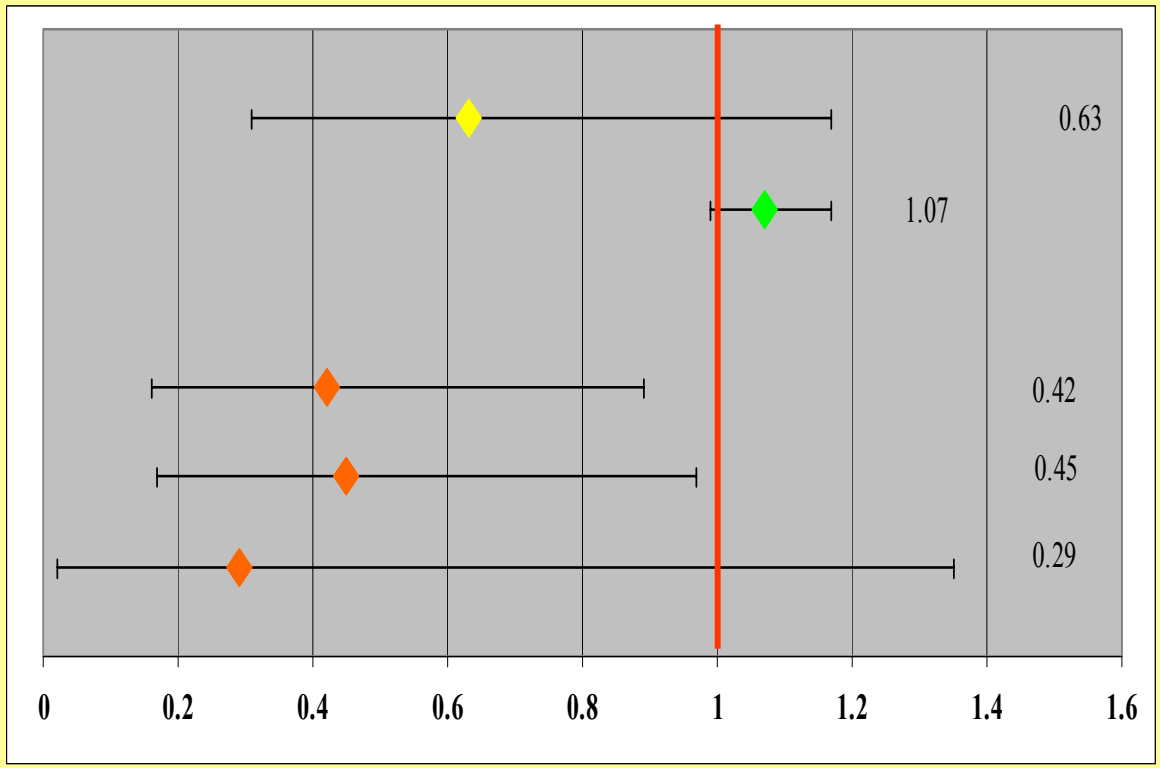
NSAIDs*

NSAIDs x Age**

NSAIDs (prior)

NSAIDs (>2 yrs)

“ (prior, >2 yrs)



*NSAIDs used at baseline; **Interaction term implies 7% increase in Hazard Ratio with each year of age.

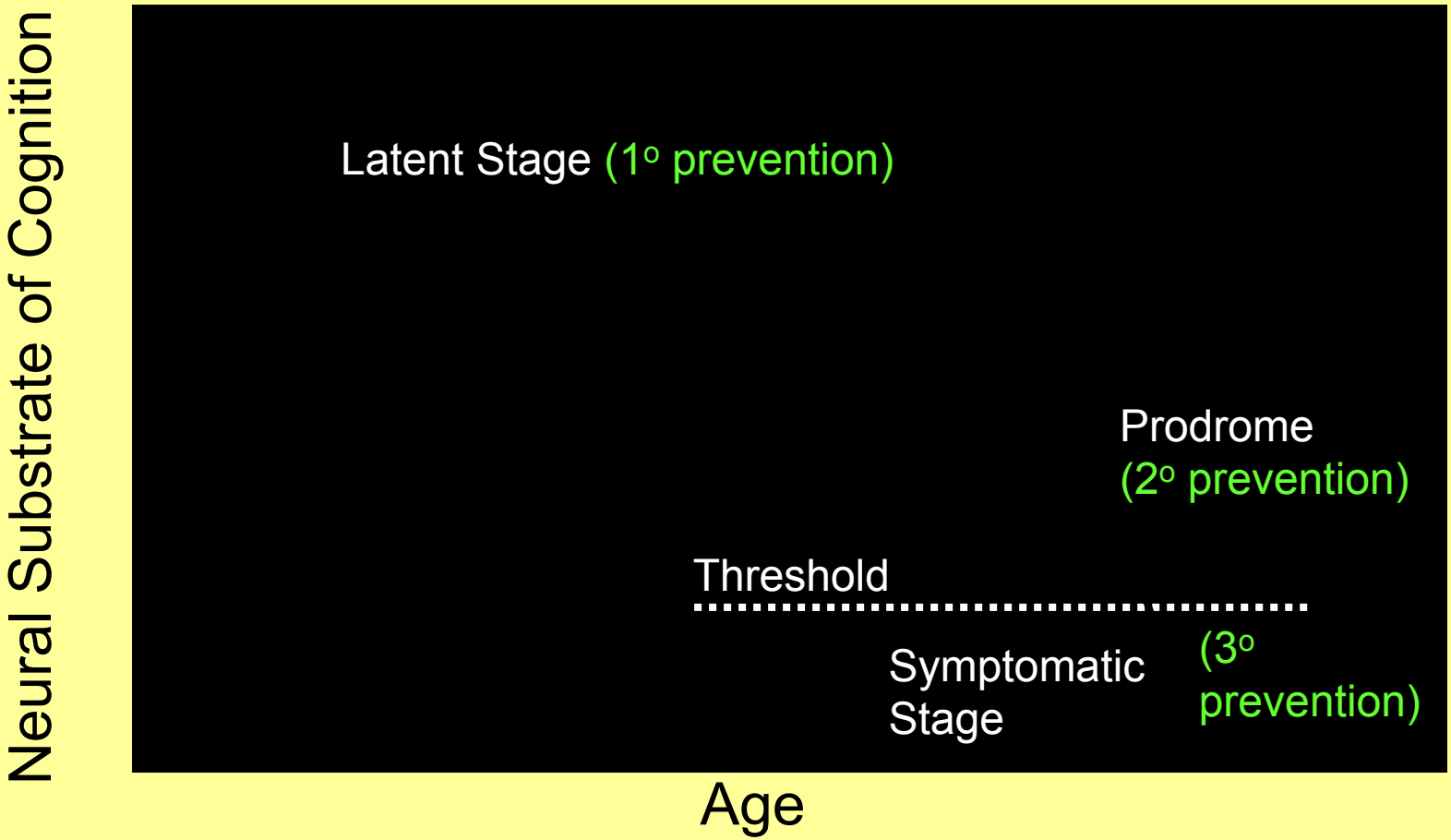
from Zandi PP, Anthony JC, Hayden KM, et al. Neurology 2002; 59:860

NSAIDs "Effect" Disappears ~2 – 3 years before onset of AD.

"Timing is Everything"

- R. M. Nixon

Potential Targets for Intervention in AD



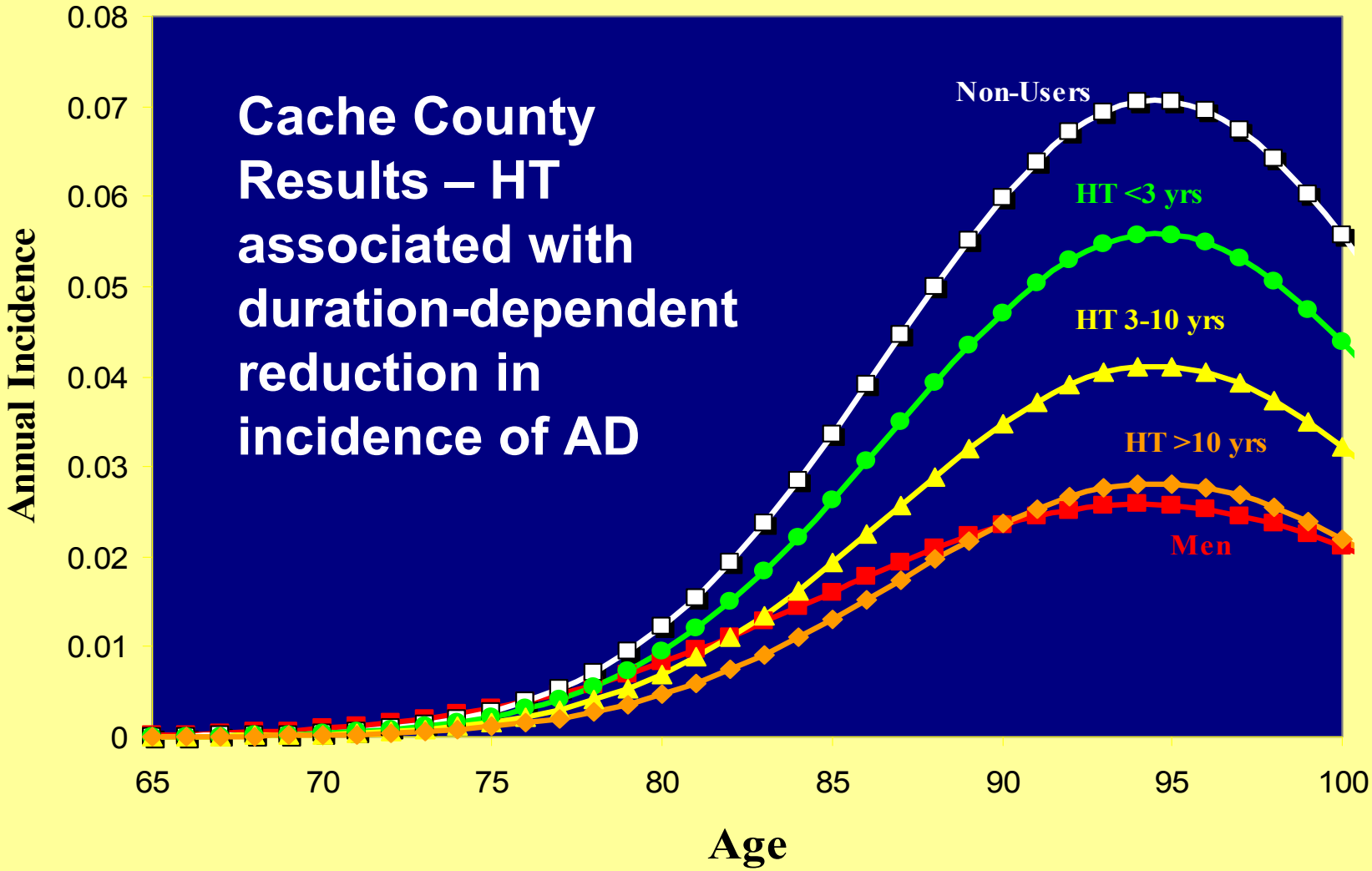
Clinical trials of NSAIDs for prevention of "conversion" from MCI to dementia will fail.

If observed, such failure will be a vindication, not a refutation, of observational study results.

HT and Dementia

- 6 Case control studies with mixed results
  - Brenner study used **10 yr.** period of observations based on periodic case detection and pharmacy dispensing records.
- 3 Prior prospective studies
  - Northern Manhattan and Baltimore Studies reflecting lifetime (mostly post-menopausal) exposures. Showed “protection”.
  - UK study based on last **10 yrs** of observations, including pharmacy dispensing records. Null.

Annual Incidence of AD (modeled)



Zandi PP, Carlson MC, Plassman BL, et al., JAMA 2002; 288:2123

But, this "effect" Depends Strongly on Timing of Hormone Exposure

- Strong effects with *prior* exposure
- No effect overall with *current* exposure
- Modest but significant decrease in risk with current exposure when duration of use exceeded 10 years, but
- Significant increase in risk with current exposures of short duration

Cache County Results vs. WHIMS – A False Contrast

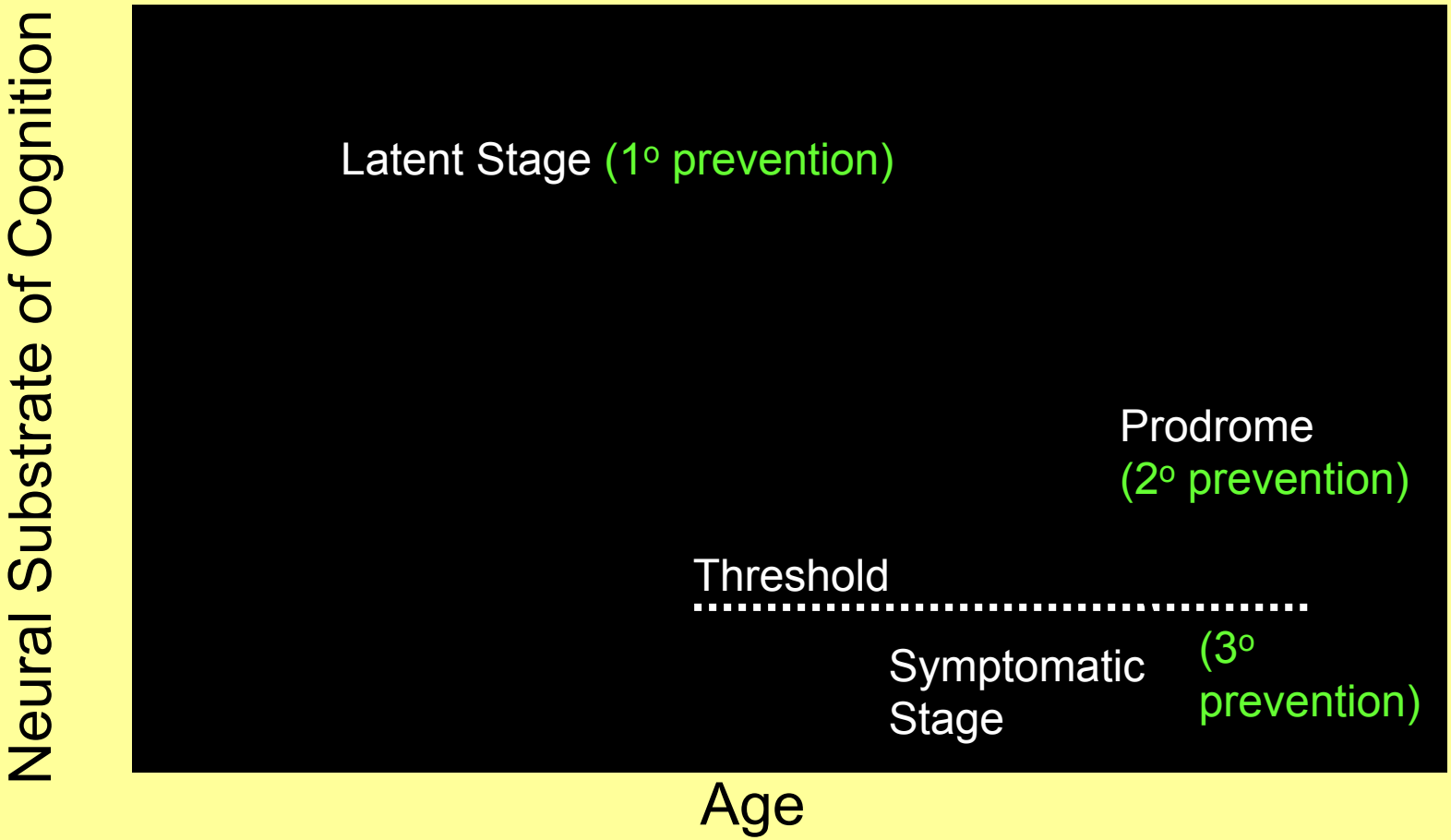
- **WHIMS adjusted hazard ratio 2.05, 95% CI 1.21 – 3.48**
- **Cache Co. current HT users**

  0 – 10 years use (n = 231) Adjusted H.R. 2.22, CI 1.05 – 4.34
- **Cache Co. former HT users (n = 229)**

  3 – 10 years use: Adjusted H.R. 0.32
  >10 years use: Adjusted H.R. 0.17 !!

Breitner JC, Zandi PP, JAMA 2003; 289:2651
Zandi PP, Carlson MC, Plassman BL, et al. JAMA 2002; 288:2123

Potential Targets for Intervention in AD



Well conducted and carefully interpreted observational studies on HT are in full accord with trials results.

Timing is, indeed, everything.

What the Observational and Trials Data Suggest about HT effects on Dementia